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EXAMINER
CAPUTA, A

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-45 are pending in the application.
   Of the above, claims 27-40 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-26 and 41-45 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Response to Amendment

1. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. Upon consideration of the amendment Groups I, II, and III are considered to one invention (i.e. Group A, claims 1-26, and 41-45). Groups IV and V are considered to be a second invention (i.e. Group B, claims 27-40).

The traversal of Groups A and B is on the ground(s) that the antibodies and the use thereof to immunize can only be obtained using a recombinant L1 major capsid protein or an antigenic fragment thereof. This is not found persuasive because either antibodies or antigen can be used for treatment of a viral immunization by a passive and active immunization respectively. Further these products (e.g. antigens and antibodies) are structurally and functionally distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. Claims 1-26 and 41-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-26 and 41-45 are vague and indefinite because as the claims are stated the recombinant L1 or antigenic portion thereof is capable of reproducing the antigenicity of all proteins found of the intact papillomavirus.

b. Claims 4-9 are rejected because it would appear that the vector comprises the DNA of the protein.

c. Claim 11, 17, 18, 21 are rejected because it is an improper Markush group.

d. Claims 1-16 and 41-45 are vague and indefinite because it is not clear of the size of the antigenic fragment. Does the applicant for instance intend to claim an antigenic fragment containing 7, 20, 100, 1000, or 10,000 amino acids.

e. Claims 25 and 26 are vague and indefinite. It is suggested the claims be changed to ".. at least one of HPV's ...".

Claim Rejections - 35 USC § 101

3. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

4. Claims 15-18, and 20-26 are rejected under 35 U.S.C. § 101 because the claimed invention as disclosed lacks patentable utility.

With regards to claims 15-18, and 20-26 the specification provides insufficient evidence that recombinantly expressed produced L1 protein or antigenic fragment thereof can prevent papillomavirus (PV) infection in humans.

Claims 15-18, and 20-26 are drawn to a LI protein of HPV for the prevention of papillomavirus infection in humans. Evidence provided is directed to the use of sera from various hosts (i.e. human, rabbit, etc) in the ability to control the cyst induced by BPV-1, bovine papillomavirus type 1 virus (see Tables 1, 11). Human sera which reacts with conformational and linear epitopes of BPV-1 did not result in the reduction of cyst (see specification, page 28). It would appear that the animal model using BPV-1 provides insufficient guidance if conformational epitopes of a recombinant L1 protein of HPV are protective in humans. When the utility of a product is directed to humans, the data must generally be clinical. In order to accept animal data, there must exist an art recognized model for testing purposes. See In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962). It is well established that a patent may not be granted on a composition unless a utility is shown other than for experimental purposes only. The burden is on the applicant to demonstrate that the claimed products posses the claimed biological activity. See Brenner v Manson 383 U.S. 519, 148 USPQ 689 (1966).

The specification further discloses that antibodies from the human sera did not prevent the infection of BPV-1 on c127 cells (see Table 3). It is not clear if the epitopes which are protective are present, secondly it is not clear that with active immunization the protective epitopes are maintained to elicit a protective immune response and finally it is not clear the antibody response to protective epitopes is sufficiently high to provide protection in vivo. The difficulty in predicting whether a particular in vitro test will be predictive of an asserted in vivo activity has long been recognized. See In re Carroll, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979).

Claim Rejections - 35 USC § 112/1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and use the claimed invention, i.e. failing to provide an enabling disclosure.

a. The specification is not enabled for the use of the claimed invention because the utility of the invention has not been proven for the same reasons outlined in the rejection under 35 U.S.C. § 101.

b. From the specification there is insufficient evidence that hosts such as cattle can elicit an antibody response recognizing conformational epitopes that provide a higher protection than antibodies recognizing linear epitopes. The specification provides evidence that monoclonal antibodies and sera of humans and vaccinated calves which recognize conformational epitopes (see Table 1) don't have a significant different mean size of cyst in comparison to the negative control (see page 28 and Table 2). It appears that polyclonal antibodies from sera of rabbits which recognize conformational epitopes is the only group which has a significantly different mean size of a cyst than the negative control (i.e. normal sera from rabbits). There is insufficient evidence that vaccinated calves or humans recognize conformational epitopes of BPV-1 or other PV'S to an extent that it provides a higher protection to PV.

The specification further teaches that not only is the L1 expressed recombinantly in cos useful for a vaccine but also for serological detection and typing (see page 48). The specification provides no evidence that a L1 expressed recombinantly is type specific for PV.

c. The specification provides insufficient guidance as to which portions of the claimed are useful for the protection of PV and are capable of reproducing the antigenicity of the intact virus. It would be expected that portions of the protein which are hydrophobic would be poorly immunogenic and not useful for the detection and/or protection of PV. Prior art at the time of the invention predicts with no certainty that a portion is antigenic. Stern teaches of the problems of predicting antigenic sites on proteins. Stern teaches that one problem of predicting antigenic sites is whether all antigenic sites on the protein in question have been found (see page 166, Column 2 and 3) and that the sequence alone is not necessarily a determinant of immunogenicity (see page 167). Berzofsky teaches that although intrinsic factors (i.e. hydrophilicity and mobility) may determine the repertoire of potential antigenic sites, only a subset of these sites will elicit antibodies (see page 937, Column 1 and 2). It would be expected therefore that the prior art teaches of potential peptides which may be antigenic sites however the identity of those peptides which are antigenic can only be determined with immunization studies.

d. The specification states that immunity for PV is type specific (see page 8, last paragraph) and that HPV's induce distinct diseases ranging from warts to cancer (see pages 2 and 41). In view of the specification teachings the demonstration of the use of a recombinant L1 for the treatment of one type of PV

is insufficient evidence that a recombinant form of L1 for other types of PV are useful for vaccination.

e. The specification provides insufficient guidance that the recombinant L1 and portions thereof are capable of reproducing the antigenicity of all proteins found of the intact papillomavirus.

6. Claims 1-26 and 41-45 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 10, 12-14, 18-21, 25 and 41 directed to the antigenic portions of the L1 protein are rejected under 35 U.S.C. § 102(b) as being anticipated by Danos et al. Danos et al. teaches of using peptides of HPV 1 type (e.g. 1a) contained in the L1 region for a vaccine. Danos et al. teaches that the

fragment can expressed by a suitable microorganism (see Column 3). Danos et al teaches (see Column 6) that the peptide can be coupled to a carrier such as serum albumins preferably animal when it relates to vaccines intended for veterinary use. It is anticipated that this includes BSA. Danos et al. further teaches (see Column 6) that the peptide can be useful for a vaccine in humans.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. Claims 1-26 and 41-45 are rejected under 35 U.S.C. § 103 as being unpatentable over Christensen et al., Pilacinski et al., Sambrook et al., and Danos et al.

Pilacinski et al. teaches of fused proteins of BPV-1, L1 and L2 cloned and expressed in E. coli. Pilacinski et al. teaches that although the antisera generated against the fusion proteins react specifically with BPV-1 to be useful as a vaccine the proteins must elicit an immunological immune response that prevents infection (see page 359, lines 1-5). Pilacinski et al. further teaches (see page 359, Column 2) that a majority of the BPV-1 specific antigenic sites were not presented to the immune system in animals and this could be due to non-natural conformation of the BPV portion. Pilacinski et al. teaches (see page 360, last paragraph) that beta-gal fusion proteins often are insoluble forming aggregates. Pilacinski et al. does not teach of expressing the L1 protein using mammalian cells to provide a L1 protein which is protective.

Christensen et al. (1990) teaches of neutralizing epitopes of HPV-11 infectious particles by monoclonal antibodies. Christensen et al. teaches the epitope(s) represent external nonlinear determinants.

It would have been obvious to one of ordinary skill in the art at the time of the invention that specific antigenic sites of L1 and L2 not presented to the immune system in animals are due to the non-natural conformation of the BPV (see Pilacinski et al.) specifically the lack of conformational epitopes, since conformational epitopes were identified as neutralizing epitopes as described by Christensen et al.

Sambrook et al. teaches (see page 16.3) that one problem of expressing proteins in bacteria is that they are folded incorrectly and consequently exhibit low specific activities. Sambrook et al. teaches a solution is the expression of proteins in mammalian cells such as SV40 and baculoviruses. Sambrook et al. teaches of several plasmid SV vectors that can be used to express the protein of interest in cos cells. It would have been obvious to one of ordinary skill in the art at the time of the invention to express the L1 protein using the method described by Sambrook et al. since it would have been expected that with the use of baculoviruses and SV40 plasmid vectors known in the art at the time of the invention the L1 would fold correctly. It would have been expected that the recombinant L1 of other PV's and other selected types of HPV would protect against the respective PV.

Danos et al. teaches (see Column 6) that the peptide can be coupled to a carrier such as serum albumins preferably animal when it relates to vaccines intended for veterinary use. It would have been obvious to couple antigenic portions of HPV using serum albumins to as described by Danos et al. to enhance immunogenicity.

Thus the claimed invention as a whole is clearly prima facie obvious, especially in the absence of evidence to the contrary.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ghim et al. teaches (see abstract) of polyclonal and monoclonal antibodies to react specifically with conformational epitopes of the HPV-1 L1 protein. Ghim et al. teaches that the screening of capsid protein of PV for reactivity with conformation dependent antibodies represents a method to ensure that such proteins will be suitable for vaccine development or detection of human PV infections..

12. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-305-7868.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0916.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4227.

Anthony C. Caputa, Ph.D.
March 7, 1993

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SUPERVISORY PATENT EXAMINER
GROUP 180